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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/734,443	10/17/1996	BRUCE A. KEYT	A-63096/WHD	1390

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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	38

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/734,443	KEYT et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18-26 and 29-35* is/are rejected.

7) ☒ Claim(s) *27 and 28* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 18-35 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 18 November 2002 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

5. Claims 18-26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a VEGF variant with a substitution of the cysteine residue at positions 51 and/or 60 with aspartic acid to inhibit disulfide bond formation, does not reasonably provide enablement for any amino acid modification of any cysteine residue as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims for the reasons of record in paper #26 and 28 as applied to claims 1-3 and 7-14, in paper #36, and for those reasons recited below.

First, it is noted that the Examiner failed to make clear the scope of enablement in the grounds of rejection. Upon reading Applicant's response, it is clear that Applicant intends any of 16 cysteine positions to be modified from the native VEGF molecule, whereas the instant specification only substitutes positions 51 and 60.

The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990) and In re Wands, 8 USPQ2d, 1400 (CAFC 1988). The factors to be considered In determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims.

The breadth of the claims is such that the claims are directed to VEGF variants which have an amino acid modification of at least one cysteine which results in an inhibition of disulfide bond formation and an antagonistic molecule. There are 16 cysteine residues in the VEGF molecule, and the modifications encompassed by the claims include amino acid substitutions and chemical

modifications of the cysteine residues. The number of structural embodiments which are encompassed by the claims is undeterminable. This is factor (8).

As to factors (4) and (6), the nature of the invention is that of protein variants which is complex and the skill in the art is assumed to be high, since the invention is in the biotech arts. The specification has working examples of substitutions of aspartic acid at positions 51 and 60, independently and in combination. Therefore, there are 3 working embodiments (factor (3)). The quantity of experimentation includes not only making the encompassed embodiments (at least 16^{19} substituted molecules, not to mention the infinite number of chemically-modified molecules), but also testing each molecule for its ability to bind the VEGF receptor and determining its ability (or lack thereof) for inducing a VEGF response (factor (1)).

The state of the prior art (factor (5)) and the predictability of the art (factor (7)) can be taken together in view of the prior art references of Claffey et al.(Biochim. Biophys. Acta. 1246(1): 1-9, 1995) and Potgens et al. (J. Biol. Chem 269(52): 32879-32885, 1994). Both of these references teach substitution of cysteine residues in VEGF to serine, which results in impaired ability to form dimers and a reduction in the ability to stimulate vascular cells. Applicant has provided evidence that these molecules of the prior art do not bind the VEGF receptor, and therefore, do not meet the functional limitations of the claims. However, these molecules clearly meet the structural limitations of the claims. Therefore, the recited structure in the claims is not sufficient for providing the required function of the claims, demonstrating the unpredictability of the claimed invention. This unpredictability is not just in the amino acid which is substituting for the cysteine, but also relates to the cysteine position which is being substituted. The prior art

teaches substitution of positions 51, 57, 60 and 61, and none of these substitution variants bind VEGF receptor, as alleged by Applicant, although they meet the structural limitations of the claims. Therefore, the prior art supports the conclusion that there is a lack of predictability for the claimed invention because clearly, the claimed structural limitations do not provide for the recited functional limitations of the claims.

The last factor to be considered in this rejection is (2) the amount of direction or guidance presented. This factor has to gauged in light of the other factors because these relate to whether there is "reasonable amount of guidance with respect to the direction in which experimentation should proceed" (*In re Wands*, as quoted by Applicant). This guidance is lacking in the instant specification. The specification would indicate that substitution or chemical modification of any of the cysteine residues in VEGF would result in a protein with the required function of the claims (antagonist molecule, which binds the receptor without inducing a VEGF response). However, this is clearly not the case since substitution with serine (prior art disclosures) does not result in this function. Therefore, the guidance/direction must be looked at in terms of what working embodiments are presented, and whether those results correlate to other modifications or whether additional modifications can be extrapolated from those results. The only examples provided in the specification which give the required function of the claims are substitution of positions 51 and/or 60 with aspartic acid. These positions are not predictive of the other cysteine positions because the other cysteine residues are in different locations, and therefore, would be expected to play a different role in receptor binding as well as in dimerization of the VEGF molecule. Mutation of these cysteine residues alone is clearly not responsible for the antagonistic properties

found with substitution of aspartic acid because the serine mutations in the prior art did not provide this function. Therefore, the guidance/direction found in the specification is limited to the working examples because the asserted "guidance/direction" would suggest substitution with another amino acid would be sufficient, and the prior art clearly demonstrates that this is not the case. Therefore, one of ordinary skill in the art would reasonably conclude that it is unpredictable which amino acids could be substituted for the cysteine residues, as well as which cysteine residues could be substituted, except for the exemplified molecules and positions with aspartic acid. In which case, the experimentation which is required to practice the claimed invention is that of making each possible structural embodiment and testing each one to see which ones work and which ones don't, without any reasonable expectation that any one particular embodiment will have the required activity. This is not an enabling disclosure, but merely an invitation to experiment.

Applicant asserts at page 3 of the response that substitution with alanine would "generally be sufficient to ascertain which of the 16 amino acid residues present in wild type VEGF could be modified to fall within the scope of the claims". This argument is not persuasive because substitution with serine should also be sufficient, and it clearly is not since the prior art molecules of Claffey et al. and Potgens et al. do not work. The ability of an amino acid to inhibit disulfide bond formation is not sufficient for providing the additional function of serving as an antagonist, therefore, each molecule would need to be tested for this functional limitation without any reasonable expectation which molecules may work and which ones may not work. This is similar to claiming VEGF antagonist, stating that mutations can be made and the activity can be tested

for. Of course the structures could be generated and the assays could be run, but the disclosure is merely an invitation to experiment since there is no reasonable expectation which direction one should proceed to arrive at the claimed invention. As in the instant case, would only cysteine residues 51 and 60 be expected to provide for the antagonistic activity or could the other cysteine residues be important. The skilled artisan does not know and could not reasonably guess based on the instant disclosure. In view of the prior art of Potgens and Claffey, one would have to say that the aspartic acid substitutions are an unexpected result and that these results could not be extrapolated to any other cysteine substitution or modification, absent evidence to the contrary.

In addition, the claims further include "modifications" of the cysteines, relating to chemical modifications which would inhibit disulfide bond formation. There is not a single example, nor is there any guidance or direction as to which chemical modifications would provide for the required functional activity of the VEGF molecules which are claimed. Therefore, the experimentation that would be required to practice the full breadth of the claims would be undue because one would not have a reasonable expectation of making a substitution or modification, expect for the substitution of aspartic acid, and obtain a functional protein with the required biological activity.

Applicant argues that substitutions could be made and the resultant protein could be tested for biological activity. However, this is merely an invitation to experiment. Such a suggestion is found in Potgens (see page 32884, column 2, paragraph 3), however, this cannot serve as a basis for a rejection over the prior art and it therefore, cannot serve as a basis for allowance of the generic claim either.

Conclusion

6. Claims 27-28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud